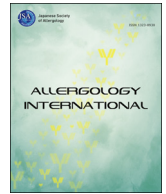


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Invited review article

## Recent developments regarding periostin in bronchial asthma

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ICS inhaled corticosteroids  
ILC2 group2 innate lymphoid cells  
FeNO fractional exhaled nitric oxide

## ABSTRACT

Although it is currently recognized that bronchial asthma is not a single disease but a syndrome, we have not yet made use of our new understanding of this heterogeneity as we treat asthma patients. To increase the efficacy of anti-asthma drugs and to decrease costs, it is important to stratify asthma patients into subgroups and to develop therapeutic strategies for each subgroup. Periostin has recently emerged as a biomarker for bronchial asthma, unique in that it is useful not in diagnosis but in categorizing asthma patients. We first found that periostin is a novel component of subepithelial fibrosis in bronchial asthma downstream of IL-13 signals. Thereafter, it was shown that periostin can be a surrogate biomarker of type 2 immune responses, the basis of the notion that a detection system of serum periostin is potentially a companion diagnostic for type 2 antagonists. Furthermore, we have recently shown that serum periostin can predict resistance or hyporesponsiveness to inhaled corticosteroids, based on its contribution to tissue remodeling or fibrosis in bronchial asthma. Thus, serum periostin has two characteristics as a biomarker for bronchial asthma: it is both a surrogate biomarker of type 2 immune responses and a biomarker reflecting tissue remodeling or fibrosis. We can take advantage of these characteristics to develop stratified medicine in bronchial asthma.

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## Introduction

It is now recognized that bronchial asthma is not a single disease but a syndrome.<sup>1</sup> Clinicians have empirically been aware of the heterogeneity of bronchial asthma for a long time. Many factors—age of onset, obesity, types of inflammatory cells, IgE-dependency, and responsiveness to inhaled corticosteroids (ICS)—lead to the heterogeneity of bronchial asthma. But as we consider treatments for asthma patients, we have not yet taken into account the heterogeneity of the disease; severity has been the most important factor in deciding on treatment.<sup>2</sup> For example, we increase the ICS dose according to severity, and for the most severely ill patients, we have other options such as oral steroids or anti-IgE antibodies. But it is now questionable whether this is the best strategy.

ICS is recognized as a very effective therapeutic agent for bronchial asthma, significantly decreasing the number of asthma deaths. However, 5–10% of asthma patients are resistant to ICS treatment.<sup>3,4</sup> Although the percentage is relatively small, these patients account for about 50% of the total medical cost of treating asthma patients. It has been reported that the effectiveness of anti-IgE antibodies for severe asthma patients is at most 60%.<sup>5</sup> Although anti-IgE antibodies recognize IgE, serum IgE levels cannot predict responsiveness. Moreover, biologics including anti-IgE antibodies are very expensive. So it is important to stratify patients into subgroups showing good or poor responsiveness to ICS or anti-IgE antibodies and to develop a strategy to administer ICS as the first-line agent and oral corticosteroids or anti-IgE antibodies as second-line agents. Development of stratified medicine in bronchial asthma would both increase the efficacy of anti-asthma drugs and decrease treatment costs.

Periostin has recently emerged as a biomarker for bronchial asthma.<sup>6</sup> Biomarkers have been mainly developed to diagnose diseases. However, periostin is a unique biomarker in that it is not used for diagnosis but for categorizing asthma patients. Diagnostics to predict the efficacy of drugs are now called “companion

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diagnostics.” So it is reasonable to expect that a periostin detection system would have the potential to be a companion diagnostic for anti-asthma drugs. In this article, we focus on the characteristics of periostin as an inflammatory mediator of bronchial asthma and the usefulness of measuring periostin in the treatment of bronchial asthma. We recommend another review article for the overall characteristics of periostin and the functional roles of periostin in allergic diseases.<sup>7</sup>

## History of the development of stratified medicine in bronchial asthma

### Anti-IL-5 antibodies

Trials for development of stratified medicine in bronchial asthma began with anti-IL-5 antibodies, although it is doubtful that the present strategy involving these antibodies was intended from the beginning. IL-5 is a signature cytokine of type 2 immune responses produced mainly in Th2 cells and group2 innate lymphoid cells (ILC2).<sup>8,9</sup> IL-5 primarily induces the development and expansion of eosinophil lineage cells. Its importance in the pathogenesis of bronchial asthma was established in the 1990s mainly through analyses of IL-5-deficient mice.<sup>10</sup> Based on these findings, anti-IL-5 antibodies were developed as anti-asthma drugs, and these agents were used in several clinical trials. However, the initial results were disappointing; although peripheral eosinophils decreased, lung functions were not improved by administering anti-IL-5 antibodies.<sup>11,12</sup> These results seem reasonable now because asthma patients are known to be heterogeneous, and molecularly targeted drugs such as anti-IL-5 antibodies would be effective only for some fraction of asthma patients, not for all. However, no stratification was performed in those trials. Thereafter, the strategy for development of an anti-IL-5 antibody called mepolizumab as an anti-asthma drug was changed, targeting steroid-resistant asthma patients showing high eosinophil numbers in sputum or blood, because it was assumed that sputum or blood eosinophils reflected IL-5 levels as a surrogate marker of IL-5. This strategy was successful, demonstrating that mepolizumab decreased exacerbation of asthma in stratified patients.<sup>13,14</sup> A phase III study of

mepolizumab has recently been reported, showing that mepolizumab has a glucocorticoid-sparing effect, reduces exacerbations, and improves asthma symptoms.<sup>15,16</sup> This study is the first example of development of stratified medicine in bronchial asthma.

### IL-4/IL-13 antagonists

The importance of IL-4 and IL-13, other signature cytokines of type 2 immune responses, in the pathogenesis of bronchial asthma was established in the 1990s using model mice, as had been done with IL-5.<sup>17–19</sup> In particular, IL-13 plays a central role in pathogenesis because compared with IL-4, it is abundantly expressed in inflamed lesions.<sup>20</sup> IL-4 and IL-13 are related cytokines sharing a receptor (type II IL-4 receptor/IL-13 receptor) and signal pathways via the receptor. Based on these findings, antagonists against IL-13, or both IL-13 and IL-4, have been developed as anti-asthma drugs. However, some antagonists have shown satisfactory results, whereas others were withdrawn for low efficacy (Fig. 1).<sup>21–26</sup> This can again be explained by the heterogeneity of asthma patients; some patients are responsive to IL-4/IL-13 antagonists, whereas others are not. Among several clinical trials, the Roche/Genentech group adopted a fruitful strategy.<sup>21</sup> They applied serum periostin as a surrogate biomarker of *in vivo* IL-13 production and examined the efficacy of an anti-IL-13 antibody called lebrikizumab for stratified patients. They found that lebrikizumab showed good efficacy for high periostin patients, whereas it did not for low periostin patients. This study should be appreciated as a milestone in the development of stratified medicine for bronchial asthma.

A Sanofi group has recently published the results of a clinical trial of an anti-IL-4 receptor  $\alpha$  chain antibody called dupilumab using peripheral or sputum eosinophils for stratification of asthma patients.<sup>23</sup> Hanania and colleagues have shown the usefulness of peripheral eosinophil number, fractional exhaled nitric oxide (FeNO), and periostin to predict the efficacy of anti-IgE antibodies (omalizumab).<sup>27</sup> More than half of the anti-asthma drugs under development are antagonists against type 2 immune responses (Fig. 2). Therefore, it is a very important issue in the establishment of stratified medicine for bronchial asthma to identify which biomarker is the most useful to reflect type 2 immune responses

Ongoing				
Antagonists	Manufacture	IL-4 Inhibition	IL-13 Inhibition	Status
Anti-IL-13 Ab (Lebrikizumab)	Roche/Genentech	-	+	phase III ongoing
Anti-IL-13Ab (Tralokinumab)	AstraZeneca/Medimmune	-	+	phase IIa finished
Anti-IL-13/IL-4 Ab (QBX258)	Novartis	-	+	phase II ongoing
Anti-IL-4R $\alpha$ Ab (Dupilumab)	Sanofi/Regeneron	+	+	phase II finished

Withdrawn				
Antagonists	Manufacture	IL-4 Inhibition	IL-13 Inhibition	Final Evaluation
IL-4 mutein (Pitrakinra)	Bayer/AEROVANCE	+	+	phase IIa
Anti-IL-4R $\alpha$ Ab (AMG 317)	Amgen	+	+	phase II
Anti-IL-13 Ab (IMA-638)	Pfizer	-	+	phase II

Fig. 1. The status of IL-4/IL-13 antagonists as anti-asthma agents. IL-4/IL-13 antagonists that are under development (upper panel) or were withdrawn (lower panel) are depicted.

Target	Agent	Form	Company	Stage
IgE M1'	Quilizumab	Antibody	Roche	P2
IgE	QGE-031	Antibody	Novartis	P2
IgE	VLP Qb-IgE vaccine	Vaccine	Cytos Biotechnology	P1
IL-13	Lebrikizumab	Antibody	Roche	P3
IL-13	Tralokinumab	Antibody	AstraZeneca	P2
IL-13	QAX-576	Antibody	Novartis	P2
IL-13	RPC-4046	Antibody	Recepto	P2
IL-13	CNTO 5825	Antibody	Janssen Biotech	P1
IL-4+13	QBX-258	Antibody + Compound	Novartis	P2
IL-4+IL-13	GSK-2434735	Bispecific antibody	GSK	P1
IL-4R	Dupilumab	Antibody	Regeneron/Sanofi	P2
IL-5	Mepolizumab	Antibody	GSK	P3
IL-5	Reslizumab	Antibody	Teva	P3
IL-5R	Benralizumab	Antibody	AstraZeneca/Kyowa Hakko Kirin	P3
Common $\beta$	CSL-311	Antibody	Hamilton/HealthCSL	P1
Common $\beta$	ASM-8	Antisense	Pharmaxis	P1
TSLP	AMG157	Antibody	Amgen/AstraZeneca	P1
CCR3	AXP1275	LMW Compound	Axilkin/Pharmaceuticals	P2
CCR4	Mogamulizumab	Antibody	Amgen/Kyowa Hakko Kirin	P2
CCR4	GSK2239633	LMW Compound	GSK	P1
CCL11	Bertilimumab	Antibody	iCO therapeutics	P1
CRTH2	QDC9101	LMW Compound	Oxigen	P3
CRTH2	ADC-3680	LMW Compound	Pulmagin Therapeutics/Teijin	P2
CRTH2	ARRY-502	LMW Compound	Array Biopharma	P2
CRTH2	QAW-039	LMW Compound	Novartis	P2
CRTH2	Actellion-3	LMW Compound	Actelion	P2
CRTH2	BI-671800	LMW Compound	Boehringer Ingelheim	P2
CRTH2	IW1221	LMW Compound	Ironwood Pharmaceuticals	P1
CRTH2	AM-461	LMW Compound	Panmira pharmaceuticals	P1

Fig. 2. Anti-asthma drugs to target type 2 responses. All anti-asthma drugs under development targeting type 2 responses are listed from the websites.

*in vivo* among several candidate biomarkers such as eosinophils, FeNO, and periostin.

### Discovery of periostin as a novel mediator of allergic airway inflammation

IL-13 is a multifunctional cytokine acting on both immune cells—B cells, macrophages, eosinophils, basophils and mast cells—and non-immune cells—epithelial cells, endothelial cells, fibroblasts, and smooth muscle cells.<sup>20</sup> Several lines of evidence have shown that the actions of IL-13 on bronchial epithelial cells are important in enhancing airway hyper-reactivity, a key feature of bronchial asthma.<sup>28,29</sup> To clarify the roles of IL-13 on human bronchial epithelial cells, we conducted a thorough search for IL-13-inducible genes using the DNA microarray method, finding that periostin is one of the highly expressed genes.<sup>30</sup> When we found these results, no relationship between periostin and inflammation or lung tissues had yet been reported.

We then investigated how periostin is involved in the pathogenesis of bronchial asthma. Using immunohistochemical analyses, we found that in asthma patients, periostin is deposited on the thickened basement membrane, suggesting that it is a component of subepithelial fibrosis in bronchial asthma (Fig. 3).<sup>31,32</sup> We confirmed that deposition of periostin is dependent on IL-4 and/or IL-13 signals: periostin deposition was significantly decreased in IL-4 or IL-13 deficient mice. This was the first formal evidence that periostin is involved in the pathogenesis of bronchial asthma.

Thereafter, Fahy and colleagues showed that periostin can be a surrogate biomarker of type 2 immune responses.<sup>33,34</sup> They classified asthma patients into “Th2-high” and “Th2-low” asthma based on expression of IL-13 and IL-5. The proportion of Th2-high asthma is estimated to be 50–70% of adult asthma.<sup>34,35</sup> They comprehensively searched for signature molecules of these two types of asthma, finding that periostin as well as chloride channel regulator 1 and serpin peptidase inhibitor, clade B, member 2, is a signature molecule of “Th2-high” asthma. This finding led to the application

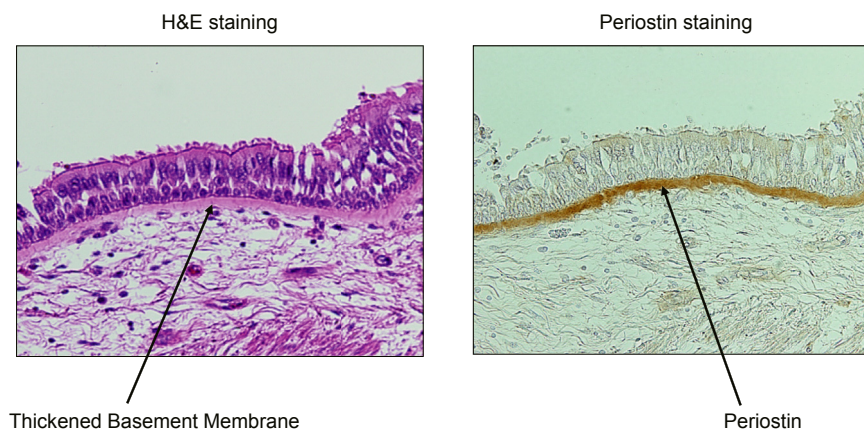


Fig. 3. Involvement of periostin in thickness of basement membrane in bronchial asthma (cited from Reference 31). Periostin is deposited on the thickened basement membrane in asthma patients.

of periostin for the stratification of asthma patients in the lebrikizumab study by the Roche/Genentech group.<sup>21</sup>

The pathological role of periostin in asthma has not yet been established. Several initial studies using periostin-deficient mice showed that periostin acts as a protective molecule against allergic airway inflammation.<sup>36,37</sup> However, it has been recently reported that periostin accelerates allergic airway inflammation, using periostin-deficient mice and neutralizing antibodies against periostin.<sup>38</sup> This discrepancy may be due to differences in the experimental protocols. We have recently evaluated the change in pulmonary functions of 20 asthma patients more than 20 years after they were first diagnosed with asthma.<sup>39</sup> We found that the degree of periostin deposition in biopsy samples obtained when they were diagnosed 20 years ago is inversely associated with their subsequent change in pulmonary function (Fig. 4), which supports the idea that periostin is an accelerator for bronchial asthma.

### Usefulness of periostin as a biomarker for bronchial asthma

#### Advantages of periostin as a biomarker

We assume that serum periostin has several advantages as a biomarker (Fig. 5). Firstly, periostin is likely to have a tendency to move easily from the affected lesions to vessels. Three types of cells—epithelial cells, fibroblasts, and endothelial cells—are possible periostin sources in bronchial asthma.<sup>31,40,41</sup> It is unsure how each type of cell contributes to up-regulation of serum periostin in asthma patients. Periostin produced in epithelial cells or fibroblasts may easily migrate into the vessels. Alternatively, periostin produced in endothelial cells may be directly secreted into the vessels. Interestingly, it is likely that little to no periostin is secreted into bronchial lumens.<sup>42</sup> Secondly, the basal level of serum periostin (~50 ng/ml) is likely appropriate as a serum biomarker. The serum levels of other ECM proteins such as fibronectin or vitronectin (~100 µg/ml) are much higher than that of periostin, which means that if the same amounts of ECM proteins migrate into vessels, increase of periostin can be easily reflected in serum periostin levels, compared to other ECM proteins. On the other hand, serum levels of cytokines including IL-13 (~100 pg/ml) are very low compared to that of periostin. Although periostin is a downstream molecule of IL-13 signals, serum IL-13 is not elevated in asthma

- Easily moves from the lesions to blood
- Basal concentration in blood is appropriate (periostin: 10–90 ng/mL)  
not too high (fibronectin/vitronectin : ~100 µg/mL)  
not too low (cytokines: ~10 pg/mL)
- A kit with low detection limit (20 pg/mL) is available

Fig. 5. Advantages of periostin as a biomarker.

patients as serum periostin is.<sup>43</sup> Lastly, several high-sensitivity ELISA kits for periostin are available. Although several commercial or non-commercial ELISA kits are in circulation, the potencies are diverse; some kits can discriminate eosinophil-dominant asthma patients, whereas others cannot.<sup>43–47</sup> Although other factors may be involved in this discrepancy, the kit itself is very important.<sup>48</sup> An ELISA kit with a low detection limit has high resolution in measuring serum periostin because we can greatly dilute the sample, decreasing the effects of other serum proteins.

#### Periostin as a surrogate biomarker of type 2 immune responses

We first measured serum periostin in overall asthma patients in the KiHAC study.<sup>44</sup> Serum periostin levels in asthma patients were significantly higher than in normal donors (asthma patients;  $n = 224$ , median: 86.0 ng/mL, average: 92.8 ng/mL, range: 22–312 ng/mL vs. normal donors;  $n = 66$ , median: 33.0 ng/mL, average: 39.1 ng/mL, range: 1–114 ng/mL). However, when the cut-off value was set at 95 ng/ml, 62% of asthma patients were within the normal range (Fig. 6). This can be explained by the

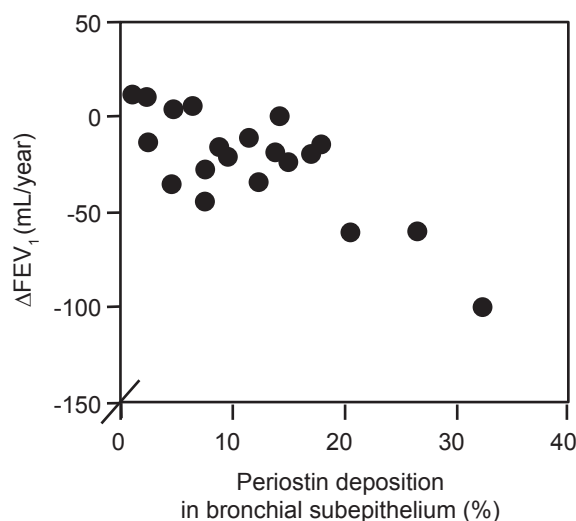


Fig. 4. Correlation between periostin deposition and decline of pulmonary function during 20 years in asthma patients (cited from Reference 39). Degree of periostin deposition in biopsy samples obtained from patients diagnosed with asthma 20 years ago is inversely associated with current pulmonary function.

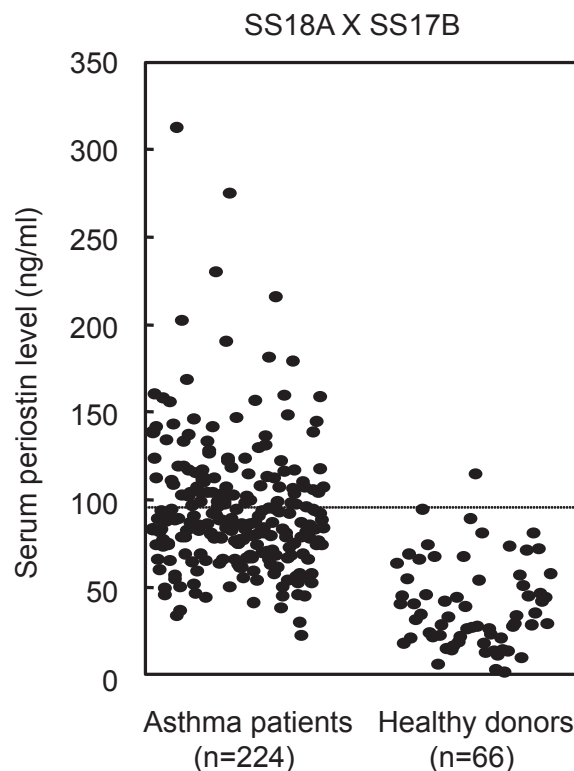


Fig. 6. Serum periostin in overall asthma patients in the KiHAC study (modified from Reference 44). Although serum periostin levels in asthma patients are significantly higher than in normal donors, when the cut-off rate was set at 95 ng/ml, 62% of asthma patients were within the normal range.

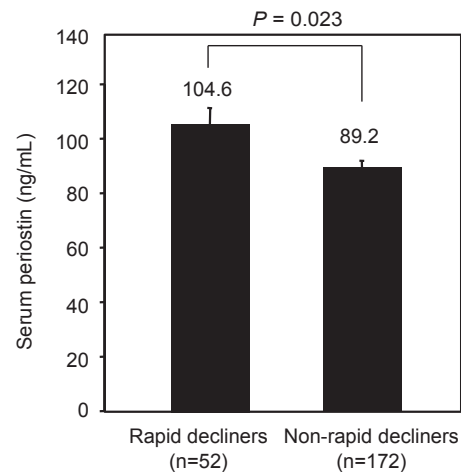


heterogeneity of asthma patients; some asthma patients show high serum periostin levels, whereas others do not. We next examined what parameter is associated with serum periostin levels, finding that late onset, blood eosinophils, serum IgE and ECP levels, and comorbidity of sinusitis show good correlation with serum periostin (Fig. 7). The association between high serum periostin and late onset, high blood eosinophil numbers, and comorbidity of sinusitis was confirmed independently by Park's group and by Asano's group.<sup>43,45</sup> Furthermore, Park and her colleagues found that aspirin-intolerant patients show high serum periostin levels.<sup>45</sup> This result was confirmed by Asano and his colleagues; when severe asthma patients were divided into high, intermediate, and low serum periostin groups, the incidence of aspirin intolerance appeared in that order.<sup>43</sup> It is well known that aspirin intolerance and chronic sinusitis/olfactory dysfunction are complications characteristic of eosinophil-dominant severe asthma.<sup>49</sup> Additionally, we have recently found that FeNO was moderately to strongly associated with serum periostin in step 4/5 patients, but only weakly in the overall patients.<sup>50</sup> As mentioned before, FeNO is another biomarker of type 2 immune responses.<sup>51,52</sup> Taken together, these results verified that serum periostin is a surrogate biomarker of type 2 immune responses. This forms the basis of the concept that serum periostin serves as a potential companion diagnostic for type 2 antagonists.

#### Periostin as a biomarker to predict hyporesponsiveness to ICS

Given that periostin contributes to tissue remodeling or fibrosis in bronchial asthma and that fibrosis is one factor causing steroid resistance in bronchial asthma,<sup>53,54</sup> we hypothesized that serum periostin can predict resistance or hyporesponsiveness to ICS. For that purpose, in the KiHAC study we divided patients into two groups, rapid decliners and non-rapid decliners.<sup>44</sup> Rapid decliners were defined as patients showing a decline in FEV<sub>1</sub> of more than 30 mL/year, indicating that these patients have some degree of hyporesponsiveness to ICS. The non-rapid decliners were defined as patients showing a decline in FEV<sub>1</sub> of less than 30 mL/year, which means these patients were good responders to ICS. Serum periostin was higher in the rapid than in the non-rapid decliners (Fig. 8). These results suggest that serum periostin is associated with hyporesponsiveness to ICS in asthma patients overall.

However, the difference of serum periostin between the rapid and non-rapid decliners was not substantial. We assumed that since asthma patients are heterogeneous, some patients would show an association between serum periostin and hyporesponsiveness to ICS, but others would not. Therefore, we next tried to categorize asthma patients and to find a subtype showing a good correlation between serum periostin and hyporesponsiveness to ICS.<sup>55</sup> We categorized asthma patients, based on their peripheral eosinophil and neutrophil counts, into four groups named clusters 1 to 4 (Fig. 9). Cluster 1, showing low numbers of eosinophils and



Rapid decliners (Poor responders) :  $\Delta\text{FEV}_1 \leq -30$  mL/year

Non-rapid decliners (Good responders) :  $\Delta\text{FEV}_1 > -30$  mL/year

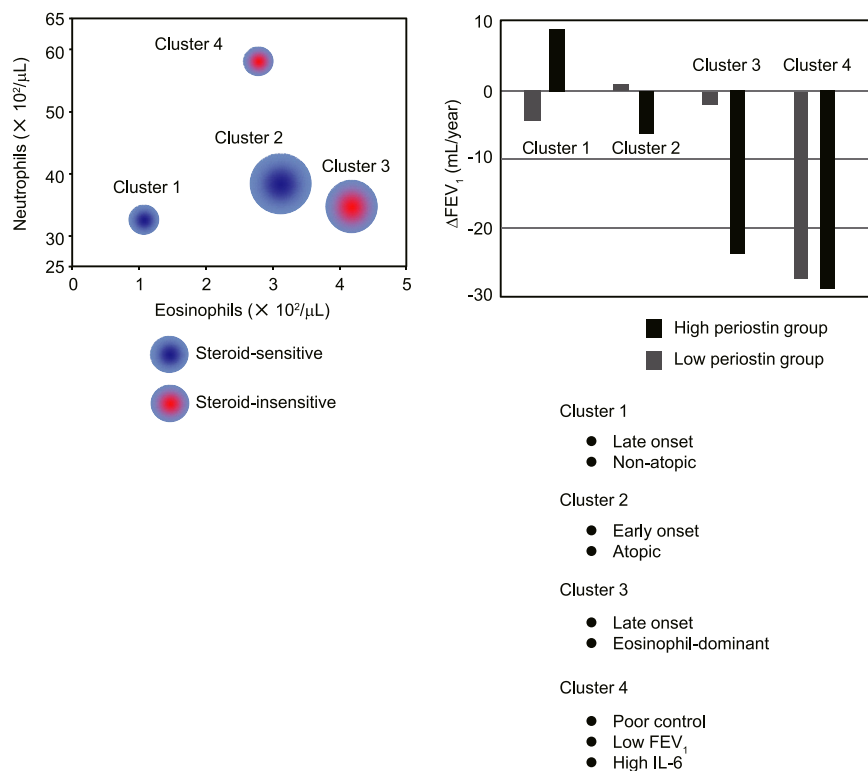
**Fig. 8.** Correlation between serum periostin and responsiveness to ICS in overall asthma patients (modified from Reference 44). Serum periostin is significantly higher in the rapid decliners (poor responders to ICS) than in non-rapid decliners (good responders to ICS).

neutrophils characterized as late-onset and non-atopic, were mostly good responders to ICS. Cluster 2, with high numbers of eosinophils characterized as early-onset and atopic, were also good responders to ICS. Cluster 3, showing higher numbers of eosinophils than cluster 2, has the characteristics of late-onset and eosinophil-dominant. The patients in this cluster included many poor responders to ICS. Cluster 4, with high numbers of neutrophils and relatively fewer eosinophils than cluster 3, had the characteristics of the poorest control and high serum IL-6 levels. Most patients in this cluster were poor responders to ICS. We then examined the correlation between serum periostin and responsiveness to ICS, in terms of changes in pulmonary function, in these clusters (Fig. 9). The patients in clusters 1 and 2 responded well to ICS, whereas the patients in cluster 4 were poor responders, irrespective of serum periostin. In cluster 3, the difference in  $\Delta\text{FEV}_1$  between high and low periostin groups was significant; the low periostin patients showed good responsiveness to ICS, whereas the high periostin patients showed poor responsiveness. Thus, by combining the categorization of peripheral eosinophil and neutrophil numbers and serum periostin, we can predict hyporesponsiveness to ICS in asthma patients.

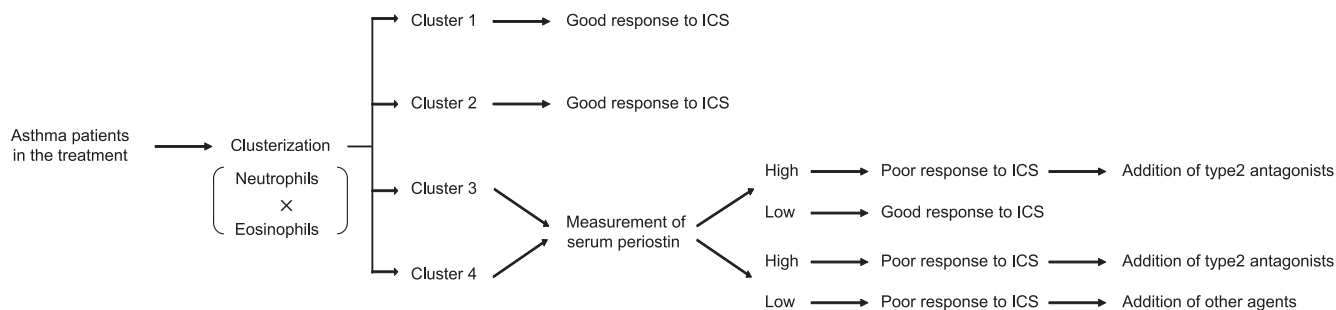
Based on these results, we propose an algorithm for treating asthma patients (Fig. 10). We recommend measuring blood eosinophil and neutrophil numbers for the patients in the treatment. It is expected that if patients belong to clusters 1 or 2, based on these measurements, they will be good responders to ICS. Next, measurement of serum periostin is highly recommended for cluster 3 and cluster 4 patients. In cluster 3, it can be expected that if they show low serum periostin, they will respond well to ICS, whereas if they show high serum periostin, they will be poor responders, with the background of Th2 inflammation, so that additional administration of type 2 antagonists should be considered. The patients belonging to cluster 4 will be poor responders to ICS. It can be expected that if they show high serum periostin, additional administration of type 2 antagonists should be considered as in the case of cluster 3. But if they show low serum periostin, administration of other agents should be considered because type 2 antagonists would be ineffective for them.

Characteristic	Reference
• Late onset	39, 43
• Eosinophil dominance	39, 43, 45
• Aspirin intolerance	43, 45
• Chronic sinusitis/Olfactory dysfunction	39, 43, 45

**Fig. 7.** Characteristics of high periostin asthma.



**Fig. 9.** Categorization of asthma patients and correlation between serum periostin and responsiveness to ICS in categorized asthma patients (cited from Reference 55). In cluster 3, defined as asthma patients with high numbers of eosinophils, the low periostin patients show good responsiveness to ICS, whereas the high periostin patients show poor responsiveness to ICS. The asthma patients in clusters 1 and 2 are good responders to ICS, and the patients in cluster 4 are poor responders to ICS, irrespective of serum periostin.



**Fig. 10.** Algorithm for treatment of categorized asthma patients. Measurement of blood eosinophil and neutrophil numbers is recommended for the patients in the treatment. The patients belonging to clusters 1 and 2 would be good responders to ICS. Measurement of serum periostin is highly recommended for both cluster 3 and cluster 4 patients. In cluster 3, the patients showing low serum periostin would be good responders to ICS, whereas the patients showing high serum periostin would be poor responders, so that additional administration of type 2 antagonists should be considered. Patients in cluster 4 would be poor responders to ICS. Additional administration of type 2 antagonists should be considered for patients showing high serum periostin, whereas administration of other agents should be considered for those with low serum periostin.

Kato *et al.* have demonstrated that stable asthma patients showing high serum periostin are at risk for instability during the tapering of ICS doses.<sup>56</sup> This result is compatible with the notion that serum periostin, as a biomarker, reflects hyporesponsiveness to ICS.

## Prospects

Evidence of the usefulness of serum periostin as a biomarker for bronchial asthma has recently accumulated. A surrogate biomarker reflecting type 2 immune responses is one characteristic of serum periostin. We can take advantage of this characteristic to predict the efficacy of type 2 antagonists. In addition, we have revealed that periostin, as a biomarker, characteristically reflects tissue remodeling or fibrosis in bronchial asthma. We can also use this

characteristic to predict hyporesponsiveness to ICS. We hope to develop and confirm the usefulness of serum periostin level as a biomarker for bronchial asthma by performing more clinical studies. It is crucial to evaluate and compare the characteristics and usefulness of other surrogate biomarkers of type 2 immune responses, eosinophils and FeNO, with serum periostin to develop stratified medicine in bronchial asthma.

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#### Conflict of interest

KI received research funding from Shino-Test Corporation, honoraria as Scientific Advisor for Chugai Pharmaceutical Co., Ltd., and a patent fee from F. Hoffmann-La Roche, Ltd. JO is an employee of Shino-Test Corporation. The rest of the authors have no conflict of interest.

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